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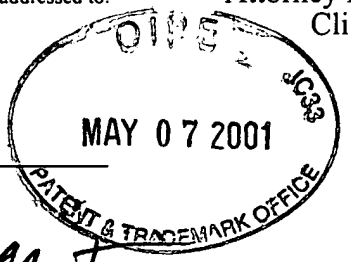
On 2 May 2001

TOWNSEND and TOWNSEND and CREW LLP

By: Malinda Dagit



PATENT
Attorney Docket No.: 015280-317100US
Client Reference No.: E-059-97/1f

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

FitzGerald *et al.*

Application No.: 09/381,497

Filed: September 20, 1999

For: RECOMBINANT ANTIBODIES AND IMMUNOCONJUGATES TARGETED TO CD-22 BEARING CELLS AND TUMORS

Examiner: Larry R. Helms, Ph.D.

Art Unit: 1642

DECLARATION OF DR. DAVID J. FITZGERALD UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. David J. FitzGerald, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true. The experimental work described herein was either conducted by myself or by a co-inventor, Dr. Ira Pastan, or under our direction.

2. I received a Ph.D. in Microbiology in 1982 from the University of Cincinnati, College of Medicine, in Cincinnati Ohio.

3. I am currently employed as the Chief of the Biotherapy Section, Laboratory of Molecular Biology in the Division of Basic Science of the National Cancer Institute at the National Institutes of Health where I conduct research relating to immunotoxins. I have authored over 170 peer-reviewed scientific publications and chapters in this area. A copy of my curriculum vitae is attached as Exhibit 1.

4. I have read and am familiar with the contents of the application. I understand that the Examiner has imposed a rejection under §112 based upon his belief that the specification does not enable the *in vivo* use of the claimed recombinant immunoconjugates to inhibit malignant B-cells *in vivo* in humans. Specifically, the Examiner appears to believe that the teachings of the specification regarding administration of the immunotoxins to humans and the evidence of *in vivo* success in mice also provided in the specification does not adequately enable the *in vivo* use of the compounds in humans. In response, I set forth below, with objective evidence, that the claimed immunoconjugates can be administered *in vivo* to humans as taught by the specification, with reasonable expectation that they will inhibit the proliferation of malignant B-cells.

5. RFB4(dsFv)-PE38 (herein referred to as BL22) is a recombinant immunotoxin that is comprised of an anti-CD22 disulfide stabilized Fv fused to a truncated *Pseudomonas* exotoxin. The disulfide-stabilized Fv has a V_H with a cysteine residue at position 44 and a V_L with a cysteine residue at amino acid position 100 as determined in accordance with the numbering system of Kabat and Wu, which is incorporated by reference in the specification of the present application. As further disclosed in the application, this immunoconjugate induced complete remissions in a murine model of human B-cell lymphoma and killed freshly obtained human leukemia cells *ex vivo*. These models are typically used in the art as predictors that a therapeutic agent will have efficacy in a human.

6. We therefore assessed the toxicity and activity of BL22 in patients with purine-resistant hairy cell leukemia in a dose-escalation trial. The results demonstrated a high response rate: of the 16 purine analog-resistant hairy cell leukemia patients treated with the immunoconjugate, 11 achieved complete remissions and 2 achieved partial responses. All 3 of the non responders received low doses of BL22 or had preexisting antitoxin antibodies.

7. The immunoconjugate was administered in a dose-escalation trial by 30 minutes intravenous infusion every other day for 3 doses to 16 patients with hairy cell leukemia, a B-cell malignancy. All patients were shown to have had $CD22^+$ malignant cells by either flow cytometry or immunohisto-chemistry. Further, the malignant disease in each of the 16 patients was resistant to standard chemotherapy. The clinical characteristics of the patients are provided in Table I, attached hereto in Exhibit 2, which comprises Tables I-III.

8. BL22 was diluted into 50 mL of 0.2 percent albumin in 0.9 percent sodium chloride and administered as a 30 minute intravenous infusion every other day for 3 doses. The cycles and doses are provided in Table II. To diminish inflammatory side effects, patients treated with dose levels of 40 μg/Kg of BL22 received the anti-TNF-α MAb Infliximab before, and one week after, the beginning of each cycle and the cyclooxygenase-2-selective nonsteroidal agent Rofecoxib 12.5 to 25 mg/day. Patients without neutralizing antibodies or progressive disease could be retreated after restaging at 3-week intervals. Patients in partial remission could receive up to 16 cycles and patients attaining complete remission could receive two additional cycles.

9. Disease was assessed by whole body computed tomography (CT), flow cytometry and PCR of blood, and histopathology of bone marrow. Determination of BL22 plasma levels and neutralizing antibodies was by cytotoxicity assay on Raji cells. Complete remission was defined as resolution of disease on radiographic studies, bone marrow biopsy and peripheral blood assessed at least 4 weeks after the last dose of BL22. All complete remissions and determination of minimal residual disease were confirmed by independent radiological review and independent blinded review of bone marrow biopsies.

10. The results of this study, shown in Exhibit 2, Table III, showed that 11 patients achieved complete remission and 2 patient achieved partial remission. All responders had normalization of radiographic findings and significant improvement in hematologic parameters. Furthermore, all responders had rapid reduction in circulating hairy cell leukemia cells, which indicates a direct cytotoxic effect of BL22. Circulating hairy cell leukemia cells were quantitated by flow cytometry. Most patients had a greater than 90% reduction by day 3 of cycle 1 and a greater than 99% reduction by day 8. To measure minimal residual disease, B- and T-cells in the marrow were assessed using immunohistochemistry with CD20 and CD3. Only one of the 11 patients in complete remission had evidence of minimal residual disease. Assessment of monoclonal B-cells by flow cytometry in the 11 patients with complete remission was negative in 10 patients. PCR studies failed to detect monoclonal B-cells in the peripheral blood in all 11 patients in complete remission.

11. Thus, as shown by the evidence prevented herein, BL22 results in inhibition of growth of malignant B-cells that express $CD22^{+}$ on the surface.

Dated: _____

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David J. FitzGerald, Ph.D.

Attachments: Exhibits 1 and 2

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